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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,585	01/13/2006	Robert S. Foote	DC0261US.NP	1514

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EXAMINER	
COUNTS, GARY W	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
05/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOactions@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/553,585	FOOTE ET AL.	
	Examiner	Art Unit	
	GARY COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/13/11 has been entered.

Currently, claims 4 and 5 are pending and under examination.

Priority

2. It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/US04/15341, filed 05/17/2004, which claims benefit of 60/474,201, filed 05/29/2003 and claims benefit of 60/501,494. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing

date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference

was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al (US 2004/0243010).

Zoghbi et al disclose determining the level of BNP in samples obtained from a patient. Zoghbi et al disclose that the patient can be suspected of having a coronary artery disease (e.g. para 0002, 0019, 0054, 0061). Zoghbi et al discloses the sample can be a blood sample (e.g. p. 9). Zoghbi et al disclose determining the level of BNP in a sample from the patient prior to exercise to establish a baseline (control) and also teaches determining the level of BNP in a sample from the same patient post exercise (abstract, pgs 9-10, particularly p. 10, Table 1, and Example 7). Zoghbi et al discloses that the levels of the BNP are determined in pg/ml before and immediately after exercise of the patient and specifically teaches an increase in the levels after exercise (e.g. see Table 1 and Example 7, lines 1-3 of paragraph 0104). Zoghbi et al specifically teaches comparing the level of BNP 13.4 pg/ml before exercise to that of 26.6 pg/ml immediately after exercise in the patient. Thus, Zoghbi et al shows an increase (change) of 13.2 pg/ml in the post exercise sample compared to the pre-exercise sample (26.6-13.4 = 13.2) (greater than 10 pg/ml)(Table 1). Zoghbi et al disclose that levels of BNP increased from baseline to post-exercise. Zoghbi et al disclose that the exercise stress test can be performed with myocardial perfusion imaging wherein a dual

isotope, rest-stress protocol is used (p. 6, para. 0070). Zoghbi et al also disclose that the lowest detectable measurement of BNP and related markers can be as low as 5 pg/ml (e.g. Example 2). Zoghbi et al explicitly teaches that the methods can be used with N-terminal probating natriuretic peptide (NTproBNP) (e.g. para 0036, 0047, 0107).

Zoghbi et al fails to specifically teach determining the absolute level of change in an individual and diagnosing based on this level in the individual. However, Zoghbi et al specifically teaches that the methods are for a patient (an individual) (e.g. abstract, para 0014, 0052, see also above) and specifically teaches a nexus between mean BNP levels in a population of patients and specifically teaches that the population of patients showed and increase of 13.2 pg/ml in the post exercise sample compared to the pre-exercise sample (26.6-13.4 = 13.2) (greater than 10 pg/ml) (Table 1). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine pre-exercise and post-exercise levels in an individual suspected of suffering ischemic cardiovascular disease and determine the absolute change in the post-exercise level compared to the pre-exercise level because Zoghbi et al specifically shows that there is increased BNP levels in post exercise ischemic patients as compared to pre-exercise patients and also specifically teaches that the methods are for the early detection and diagnosis of coronary artery disease in a patient (abstract). Therefore, one of ordinary skill would have a reasonable expectation of success incorporating the teaching of Zoghbi et al for determining an absolute BNP change in pre-exercise and post exercise in an individual and detecting cardiac ischemia in the individual.

Response to Arguments

7. Applicant's arguments filed 04/13/11 have been fully considered but they are not persuasive.

Applicant argues that Zoghbi et al disclose use of an entirely different endpoint for assessing risk of ischemia in patients, including the method involving measurement of blood levels of BNP in the same patient both before and after exercise as taught in Examples 5-7, Table 1, page 9-10. Applicant states that although BNP increased from baseline to immediately post exercise in individuals with ischemia as well as those without ischemia, the actual pg/ml change in BNP levels post exercise in patients either with or without ischemia had a median value of 15.5 pg/ml in ischemia patients, i.e. patients diagnosed with ischemia, and that the difference between the change in pg/ml of BNP between ischemic patients and those identified as being not ischemic was not statistically significant (p-value reported to be 0.115).

This is not found persuasive because the argument is not on point, as stated in the previous office actions this comparison is between non-ischemic patients vs. ischemic patients (i.e. sample from different patients). Further, as stated above Zoghbi specifically teaches a nexus between mean BNP levels in a population of patients and specifically teaches that the population of patients showed and increase of 13.2 pg/ml in the post exercise sample compared to the pre-exercise sample (26.6-13.4 = 13.2) (greater than 10 pg/ml) (Table 1). It is noted that this nexus is determined is in ischemic patients vs. ischemic patients (see Table 1) and is not a comparison of non-ischemic patients vs. ischemic patients as referred to by Applicant.

Applicant argues that the language in the patent is also very important as it provides one of skill with the expectation of no success in using absolute levels of BNP or NTproBNP. Applicant states that the application states "Neither the absolute BNP levels at peak nor the absolute level of rise from baseline to immediate post-exercise differentiated between ischemic and non-ischemic patients." (para 0104). Applicant states that this is an important teaching in Zoghbi et al that speaks to a lack of motivation and also of an expectation of success to modify the method of the reference to employ a measure of an absolute change in a blood level of either BNP or NTproBNP in lieu of use of percent change in blood levels of BNP, as is explicitly taught by Zoghbi et al as being the useful measure in populations of patients.

This argument is not found persuasive because once again Applicant is referring to a comparison between non-ischemic patients vs ischemic patients. As stated above and in the previous office actions the Examiner has relied upon the teachings of Table 1 comparing ischemic patients vs ischemic patients. Zoghbi specifically teaches a nexus between mean BNP levels in a population of patients and specifically teaches that the population of patients showed and increase of 13.2 pg/ml in the post exercise sample compared to the pre-exercise sample (26.6-13.4 = 13.2) (greater than 10 pg/ml) (Table 1).

Applicant further argues that nowhere does Zoghbi et al disclose the actual magnitude of changes in blood levels of BNP in an individual patient after exercise as compared to before exercise. Applicant argues that Zoghbi et al fails to provide a

motivation to use a different method and endpoint, a method based on absolute changes in blood levels in individuals versus a percent change in a population.

These arguments are not found persuasive because although the increase of 13.2 (26.6 – 13.4 = 13.2) shown in the post exercise ischemic patients from that of the pre-exercise ischemic patients in para 0102 and Table 1 is a mean value of the ten patients and is directed to a value obtained from a population of patients. Zoghbi e al teaches that the methods are to be used for detecting in an individual and specifically teaches that there is a nexus for increase BNP levels post exercise as compared to pre-exercise levels and it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine pre-exercise and post-exercise levels in an individual suspected of suffering ischemic cardiovascular disease and determine the absolute change in the post-exercise level compared to the pre-exercise. Thus, for the reasons stated above it is the Examiner's position that the reference explicitly provide the motivation needed for the rejection. However, it is noted that while it is true that when obviousness is based on a particular prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference; it is also true that this suggestion or motivation need not be expressly stated. Cable Elec. Prods., Inc. v. Genmark, Inc., 770 F.2d 1015, 1025, 226 U.S.P.Q. 881, 886 (Fed. Cir. 1985). The conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art without any specific hint or suggestion in a particular reference.

Applicant further argues that Zoghbi et al fails to provide a reasonable expectation of success because, as demonstrated by the data presented by Zoghbi in Example 7 there was a wide variability in the baseline levels and post-exercise levels of BNP among subjects, at least a three-fold level of variability (para 0104). Applicant states that it is this wide range within a population that fails to provide one of skill in the art with an expectation that there would reliably a response in an individual that meets the criteria of the instant invention of absolute changes of only 10 pg/ml for BNP or 5 pg/ml for NTproBNP.

These arguments are not found persuasive because once again the Applicant is relying on an embodiment that is not relevant to the instant claims. Example 7 is a comparison between non-ischemic patients vs. ischemic patients (i.e. sample from different patients). The Examiner has relied upon Zoghbi showing in Table 1 of BNP levels in pre-exercise ischemic patients and post-exercise ischemic patients and showing an increase of 13.2 (26.6 – 13.4 = 13.2) shown in the post exercise ischemic patients from that of the pre-exercise ischemic patients in para 0102 and Table 1. (same patients). Therefore, since Zoghbi et al specifically teaches that the methods are for a patient (an individual) (e.g. abstract, para 0014, 0052, see also above) and specifically teaches a nexus between mean BNP levels in a population of patients and specifically teaches that the population of patients showed and increase of 13.2 pg/ml in the post exercise sample compared to the pre-exercise sample (26.6-13.4 = 13.2) (greater than 10 pg/ml) (Table 1). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine pre-exercise and post-exercise levels

in an individual suspected of suffering ischemic cardiovascular disease and determine the absolute change in the post-exercise level compared to the pre-exercise level because Zoghbi et al specifically shows that there is increased BNP levels in post exercise ischemic patients as compared to pre-exercise patients and also specifically teaches that the methods are for the early detection and diagnosis of coronary artery disease in a patient (abstract). Therefore, one of ordinary skill would have a reasonable expectation of success incorporating the teaching of Zoghbi et al for determining an absolute BNP or NTproBNP change in pre-exercise and post exercise in an individual and detecting cardiac ischemia in the individual and one would also expect the values in pg/ml to be greater than 5 pg/ml in NTproBNP because Zoghbi et al teaches the lowest level of detection to be 5 pg/ml.

Applicant argues that the claims have been amended to recite that the methods of the present invention are "consisting of" the specific cited steps and nowhere does Zoghbi et al teach the specific steps cited. This argument is not found persuasive because of reasons stated above it would have been obvious to one of ordinary skill in the art at the time the invention was made determine pre-exercise and post-exercise levels in an individual suspected of suffering ischemic cardiovascular disease and determine the absolute change in the post-exercise level compared to the pre-exercise level because Zoghbi et al specifically shows that there is increased BNP levels in post exercise ischemic patients as compared to pre-exercise patients and also specifically teaches that the methods are for the early detection and diagnosis of coronary artery disease in a patient (abstract). Therefore, one of ordinary skill would have a reasonable

expectation of success incorporating the teaching of Zoghbi et al for determining an absolute BNP change in pre-exercise and post exercise in an individual and detecting cardiac ischemia in the individual. Thus, the recited steps have been met.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/

Examiner, Art Unit 1641